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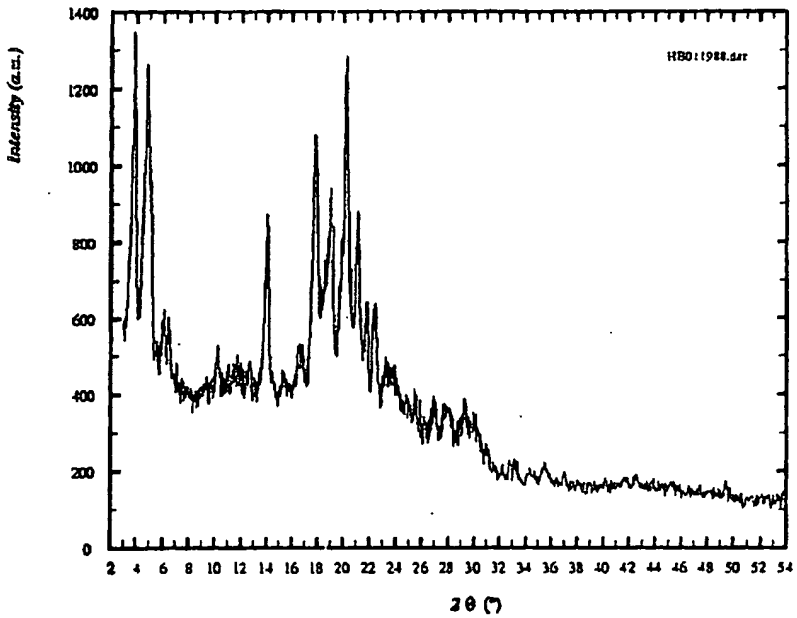
[Continued on next page]

(54) Title: NOVEL FORM OF N-(TRANS-4-ISOPROPYLCYCLOHEXYLCARBONYL)-D-PHENYLALANINE



(57) Abstract: Novel polymorph Form C of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is produced having different infra red spectrum and X-ray diffraction patterns from previously known forms of the compound.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Novel Form Of
N- (trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine

FIELD OF THE INVENTION

The present invention relates to a novel crystalline form of N- (trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine and a process for preparing the same.

BACKGROUND OF THE INVENTION

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine has therapeutic utility in depressing blood glucose levels in the management of Type 2 diabetes mellitus.

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is disclosed in Japanese Patent Application No. 63-54321 (equivalent to EP-A-196222 and US 4,816,484). The Japanese application describes how the compound may be crystallized from aqueous methanol to yield crystals having a melting point of 129°C to 130° C. These crystals are referred as "B-type". These B-type crystals suffer from problems of instability, especially when subjected to mechanical grinding.

J. Med. Chem. 32, 1436 (1989) discusses preparation of N-(cyclohexylcarbonyl)-D-phenylalanines and related compounds which includes N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

US Patent Nos. 5,463,116 and 5,488,150 discloses preparation of novel crystalline form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine designated "H-type". This patent also discloses a method of treating form "B" crystals with appropriate solvent mixtures to obtain form "H" crystals and vice-versa. The H-type crystals have an enhanced stability over B type crystals.

Yaowu Fenxi Zazhi 2001, 21, 342 discusses "S" form of nateglinide which is different from form "B" and form "H".

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided a novel process for the production of novel crystalline form "C" of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine by reacting D-phenylalanine methylester HCl with *trans-4*-isopropylcyclohexane carboxylic acid in presence of propane phosphonic acid anhydride or $LiOH\text{-}Al_2O_3$ in halogenated hydrocarbon solvents such as dichloromethane, dichloroethane at a temperature between -10° C to 90° C followed by base hydrolysis.

Alternatively, the product can be obtained by reacting *trans-4*-isopropylcyclohexane carbonyl chloride with D-phenylalanine methylester HCl in halogenated hydrocarbon solvents such as dichloromethane, dichloroethane in presence of base such as triethylamine, pyridine at a temperature between -10°C to 90° C followed by base hydrolysis.

According to a still further aspect of the present invention, the new crystal from "C" of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine thus produced have at least one, and preferably all, of the following properties:

(a) a melting point in the range of 126 °C to 132 °C;

(b) a powder X-ray diffraction pattern comprising characteristic peeks at 14.0, 17.8, 19.0, 20.2 and 21.2 $\pm$ 0.2 degrees measured at reflection angle 2θ;

(c) an infrared absorption spectrum comprising absorption bands at with absorption bands in the region of 1742, 1648, 1599, 1540 and 1191 $\pm$ 2 cm^{-1}.

Yet another aspect of the invention includes a N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine Form C for use in the preparation of a medicament for treating Type 2 diabetes mellitus.

This invention also includes a pharmaceutical composition comprising a therapeutically effective amount of crystals of Form C N-(trans-4-isopropylcyclohexylcarbonyl)-D-Phenylalanine.

Another aspect of the invention, relates to a method for treating patients suffering from type 2 diabetes mellitus by administering a therapeutically effective amount of the pharmaceutical composition of Form C of N-(trans-4-isopropylcyclohexylcarbonyl)-D-Phenylalanine.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

FIG. 1 shows a powder X-ray diffraction pattern of form C crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine;

FIG. 2 shows an infra red absorption spectrum of form C crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine;

DETAILED DECSRIPTION OF THE INVENTION

The process according to the inventors for preparing N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine form C comprises

(a) suspending N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester in water or a water miscible solvent;

(b) treating the suspension with a base;

(c) addition of water followed by adjusting the pH to 1.0-4.0 using a mineral acid;

(d) extracting using ethyl acetate;

(e) concentrating the ethyl acetate extract;

(f) addition of petroleum ether to the ethyl acetate concentrate; and

(g) filtering and drying the precipitate obtained to get N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine form C.

The water miscible solvent in step (a) is selected from methanol, ethanol, isopropanol, or a mixture of these, preferably methanol. The base in step (b) is selected from potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide or a mixture of these preferably potassium carbonate.

The precipitate obtained in step (g) is suspended in water before filtration and drying to get N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine form C.

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester is prepared by:

- reacting D-Phenylalanine methyl ester hydrochloride with trans-4-isopropylcyclohexane carboxylic acid in the halogenated hydrocarbons
- filtering the reaction mixture;
- concentrating to get N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester.

The first step in the above process for the preparation of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester is carried out in the presence of propane phosphonic acid anhydride, LiOH adsorbed in aluminium oxide or triethylamine.

An alternate method for producing N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester comprises the steps of

- reacting D-Phenylalanine methyl ester hydrochloride with trans-4-isopropylcyclohexane carbonyl chloride in halogenated hydrocarbon solvents and in the presence of a base,
- filtering the reaction mixture;
- concentrating to get N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester.

The halogenated hydrocarbon solvents are selected from dichloromethane or dichloroethane.

The base are selected from triethylamine or pyridine. The the reaction temperature is -10 ° to 90 ° C.

Embodiments of the invention are illustrated below by way of the following examples, not to be considered as limiting.

EXAMPLE 1

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester:

D-Phenylalanine methyl ester hydrochloride (10g, 0.046 mol) was suspended in a solution of triethylamine (33 mL) in dichloromethane (50 mL); the mixture was cooled to 0-5 °C and trans-4-isopropylcyclohexane carboxylic acid (7.9 g, 0.046 mol) was added to the reaction mixture. A solution of Propane phosphonic acid anhydride (46.4 mL, 0.046 mol) in ethyl acetate was added dropwise over a period of 30 minutes, maintaining the temperature at 0-5 °C and stirred for 14 hours at ambient temperature. The reaction mixture was washed with 1.5 N HCl, 5% sodium bicarbonate solution and brine. The organic layer was concentrated to yield 12.5 g of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester.

EXAMPLE 2

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester:

D-Phenylalanine methyl ester hydrochloride (20g, 0.092 mol) was suspended in a solution of triethylamine (66 mL) in dichloroethane (100 mL) and the mixture was stirred for 1 h at room temperature. The organic layer was separated after washing with water and dried over anhydrous sodium sulphate. trans-4-Isopropylcyclohexane carboxylic acid (15.8 g, 0.092 mol) was added to the organic layer followed by $LiOH-Al_2O_3$ (5.5g of LiOH adsorbed on 40.5g Aluminum oxide) and refluxed for 24 hours. The reaction mixture was filtered over celite bed and washed with 1.5 N HCl, 5% sodium bicarbonate solution and brine. The organic layer was concentrated to yield 15.5 g of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester.

EXAMPLE 3

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester:

D-Phenylalanine methyl ester hydrochloride (26g, 0.12 mol) was suspended in a solution of triethylamine (85 mL) in dichloromethane (125 mL) and the mixture was cooled to 0-5 °C. A solution of trans-4-isopropylcyclohexane carbonyl chloride (25g, 0.13 mol) in dichloromethane (75 mL) was added dropwise over a period of 10 minutes, maintaining the temperature at 0-5° C and stirred for 12 hours at ambient temperature. The reaction mixture was washed with 1.5 N HCl, 5% sodium bicarbonate solution and brine. The organic layer was concentrated to yield 38g of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester.

EXAMPLE 4

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine:

To suspension of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester (38 g, 0.11 mol) in methanol (600 mL), a solution of potassium carbonate (80g, 0.57 mol) in water (400 mL) was added and the reaction mixture was stirred for 12 h at ambient temperature. Water (1500 mL) was added and pH was adjusted to 2.0 by adding 6N HCl. The mixture was extracted using ethyl acetate (3 x 400 mL) and the combined extract was washed with brine. The organic layer was concentrated to about 150 mL and pet. ether (300 mL) was added. The product was filtered and suspended in water (600 mL) and stirred for 12 hours at ambient temperature. The slurry was filtered and dried to yield 35g of the title compound.

The compound showed a sharp melting point of 128 – 129 °C. X-ray diffraction pattern and infra red absorption spectrum of the final compound was recorded and identified as form C crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

We claim:

1. Crystalline N-(trans-4-isopropylcyclohexylcarbonyl)-D-Phenylalanine having at least one of the following properties:
   (a) a melting point in the range of 126° to 132 ° C;
   (b) a powder X-ray diffraction pattern comprising characteristic peeks at 14.0, 17.8, 19.0, 20.2 and 21.2 $\pm$ 0.2 degrees measured at reflection angle 2θ;
   (c) an infrared absorption spectrum comprising absorption bands at with absorption bands in the region of 1742, 1648, 1599, 1540 and 1191 $\pm$ 2 cm^{-1}.

2. N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine Form C.

3. N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine Form C for use in the preparation of a medicament for treating Type 2 diabetes mellitus.

4. A process for preparing N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine form C comprising the steps of:
   (d) suspending N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester in water or a water miscible solvent;
   (e) treating the suspension with a base;
   (f) addition of water followed by adjusting the pH to 1.0-4.0 using a mineral acid;
   (d) extracting using ethyl acetate;

(e) concentrating the ethyl acetate extract;

(f) addition of petroleum ether to the ethyl acetate concentrate;

(g) filtering and drying the precipitate obtained to get N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine form C.

5. A process of claim 4 wherein the water miscible solvent in step (a) is selected from methanol, ethanol, isopropanol, or a mixture of these.

6. A process of claim 5 wherein the water miscible solvent in step (a) is methanol.

7. A process of claim 4 wherein the base in step (b) is selected from potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide or a mixture of these.

8. A process of claim 7 wherein the base in step (b) is potassium carbonate.

9. A process of claim 4-8 wherein the precipitate obtained in step (g) is suspended in water before filtration and drying to get N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine form C.

10. A process of claim 4 wherein N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester of step (a) is prepared by:

- reacting D-Phenylalanine methyl ester hydrochloride with trans-4-isopropylcyclohexane carboxylic acid in the halogenated hydrocarbons

- filtering the reaction mixture;
- concentrating to get N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester.

11. A process of claim 10 wherein said halogenated hydrocarbon solvents are selected from dichloromethane or dichloroethane.

12. A process of claim 10 wherein step (a) is carried out in the presence of propane phosphonic acid anhydride, LiOH adsorbed in aluminium oxide or triethylamine.

13. A process of claim 4 wherein N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester of step (a) is prepared by:

- reacting D-Phenylalanine methyl ester hydrochloride with trans-4-isopropylcyclohexane carbonyl chloride in halogenated hydrocarbon solvents and in the presence of a base,
- filtering the reaction mixture;
- concentrating to get N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine methyl ester.

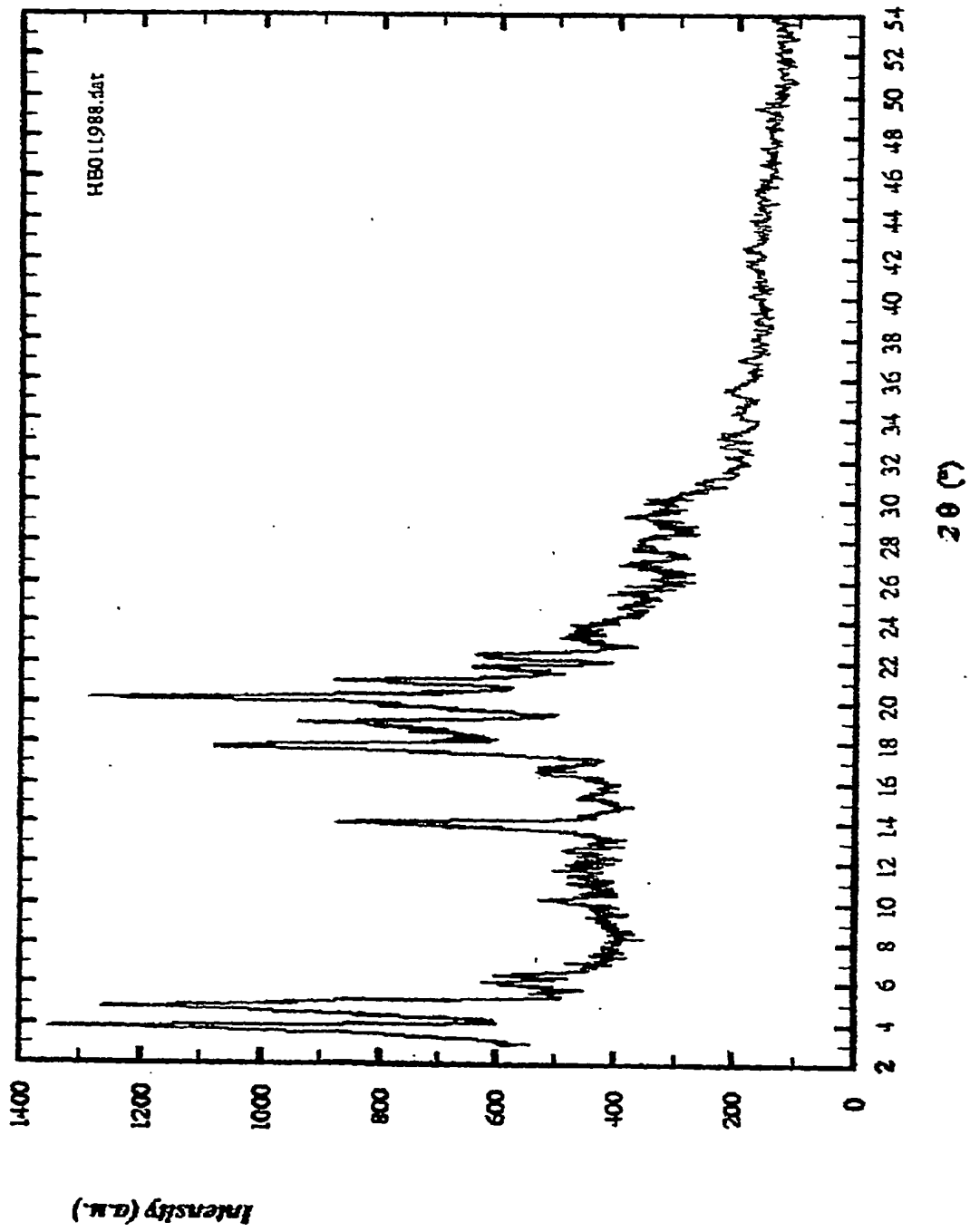
14. A process of claim 13 wherein said halogenated hydrocarbon solvents are selected from dichloromethane or dichloroethane.

15. A process of claim 13 wherein said base are selected from triethylamine or pyridine.

16. A process of claim 10 or 13 wherein the reaction temperature is -10 ° to 90 ° C.

17. A pharmaceutical composition comprising a therapeutically effective amount of crystals of Form C N-(trans-4-isopropylcyclohexylcarbonyl)-D-Phenylalanine according to claim 1.

FIG 1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Intensity (a.u.)
2θ (°)
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600
800
1000
1200
1400
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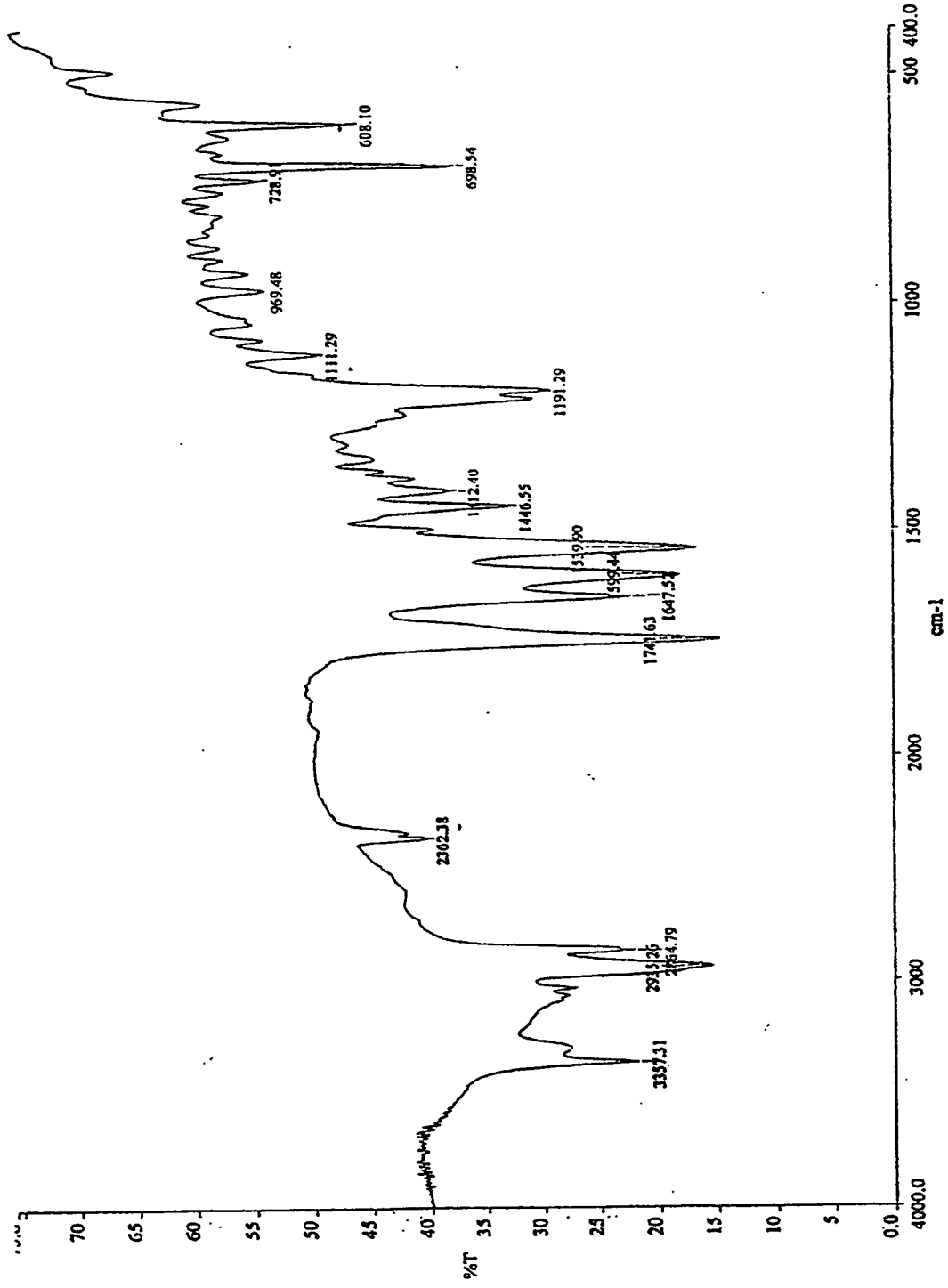
FIG 2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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN02/00114

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07C 233/63; A61K 31/198

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN: Chemical Abstracts; based on the compound of the invention in the claims

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 196 222 B1 (AJINOMOTO CO., INC.) 1 October 1986 See example 31, (m.p.). (& US 4,816,484 A)	1-17
X	Shinkai H et al.: "N-(Cyclohexylcarbonyl)-D-phenylalanines and Related Compounds. A New Class of Oral Hypoglycemic Agents. 2"; Journal of Medicinal Chemistry, 1989, Vol. 32 NO. 7, pp 1436-41. See table II, compound 13	1-17
A	US 5,463,116 A (Sumikawa et al.) 31 October 1995 Whole document	1-17

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

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5 September 2002	17 SEP 2002
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN02/00114

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts 136:159110; Li G et al.: "A new crystal structure in nateglinide found by X-ray powder diffraction"; Yaowu Fenxi Zazhi (2001), 21(5), 342-344 Abstract	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN02/00114

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
EP	196222	US	4816484	JP	63054321		
US	5463116	BR	1100807	CA	2114678	EP	526171
		LU	90843	LU	90846	US	5488150
		JP	5208943				

END OF ANNEX